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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 263/58, 213/74, A61K 31/42, 31/44 — A1

(11) International Publication Number: WO 96/04260

(43) International Publication Date: 15 February 1996 (15.02.96)

(21) International Application Number: PCT/EP95/03038

(22) International Filing Date: 28 July 1995 (28.07.95)

(30) Priority Data:

9415330.1	29 July 1994 (29.07.94)	GB
9425599.9	19 December 1994 (19.12.94)	GB
9509923.0	17 May 1995 (17.05.95)	GB
PCT/GB95/01323	7 June 1995 (07.06.95)	WO

(34) Countries for which the regional or international application was filed: GB et al.

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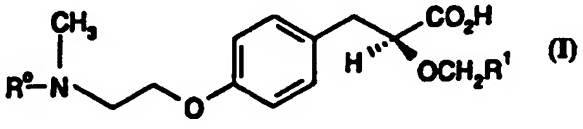
(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).

Published
With international search report.

(54) Title: BENZOXAZOLES AND PYRIDINE DERIVATIVES USEFUL IN THE TREATMENT OF THE TYPE II DIABETES

(57) Abstract

A compound of formula (I) or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein R^o represents 2-benzoxazolyl or 2-pyridyl and R^1 represents CH_2OCH_3 or CF_3; a process for the preparation of such compounds, a pharmaceutical composition containing such compounds and the use of such compounds and compositions in medicine.



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BENZOXAZOLES AND PYRIDINE DERIVATIVES USEFUL IN THE TREATMENT OF THE TYPE II DIABETES

This invention relates to certain novel compounds, to a process for preparing such compounds, to pharmaceutical compositions containing such compounds and to the use of such compounds and compositions in medicine.

International Patent Application, Publication Number WO 94/01420 discloses compounds of formula (A):

$$A^{1'}\text{-}X'\text{-}(CH_2)_{n'}\text{-}O\text{-}A^{2'}\text{-}A^{3'}\text{-}Y.R^{2'} \qquad (A)$$

or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:

$A^{1'}$ represents a substituted or unsubstituted aromatic heterocyclyl group;

$A^{2'}$ represents a benzene ring having three optional substituents;

$A^{3'}$ represents a moiety of formula $-(CH_2)_m-CH(OR^{1'})-$ wherein $R^{1'}$ represents substituted or unsubstituted alkyl, aryl, aralkyl or alkylcarbonyl and m represents an integer in the range of from 1 to 5, or $A^{3'}$ represents a moiety of formula $-(CH_2)_{m'-1}-CH=C(OR^{1'})-$ wherein $R^{1'}$ and m' are as defined above;

$R^{2'}$ represents $OR^{3'}$ wherein $R^{3'}$ represents hydrogen, alkyl, aryl or aralkyl or $R^{2'}$ represents an aromatic heterocyclyl group or $-NR^{4'}R^{5'}$ wherein $R^{4'}$ and $R^{5'}$ each independently represent hydrogen, alkyl or alkylcarbonyl or $R^{4'}$ and $R^{5'}$ together with the nitrogen atom to which they are attached form a heterocyclic ring, providing that $R^{2'}$ represents an aromatic heterocyclyl group only when Y' as defined below represents a bond ;

X' represents NR' wherein R' represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;

Y' represents C=O or C=S or a bond providing that Y' represents a bond only when $R^{2'}$ represents the above mentioned aromatic heterocyclyl group; and

n' represents an integer in the range of from 2 to 6.

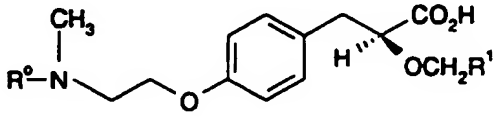
These compounds are stated to have *inter alia* good blood-glucose lowering activity and are therefore of potential use in the treatment and/or prophylaxis of hyperglycaemia and to be of particular use in the treatment of Type II diabetes.

It has now surprisingly been discovered that a particular group of compounds falling within the generic scope of the compounds of formula (A) have particularly good blood-glucose lowering activity combined with freedom from adverse haematological and cardiac effects. These compounds are therefore c nsidered to hold potential to be of particular use in the treatment and/or prophylaxis of hyperglycaemia and to be of particular use in the treatment of Type II diabetes.

These compounds are also indicated to be of potential use for the treatment and/or prophylaxis of other diseases including hyperlipidaemia and hypertension. They are also indicated to be of use in the treatment and/or prophylaxis of cardiovascular disease, especially atherosclerosis. In addition these compounds are considered to be useful for treating certain eating disorders, in particular the regulation of appetite and food intake in subjects suffering from disorders associated with under-eating, such as anorexia nervosa, and disorders associated with over-eating, such as obesity and anorexia bulimia.

These compounds are also indicated to be of of potential use in the treatment and/or prophylaxis of renal disease, especially renal disease associated with the development of Type II diabetes including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease. The prophylactic action of an insulin sensitiser upon nephropathy is also indicative that an insulin sensitising agent can be expected to prevent, reverse, stabilise or retard the progression of microalbuminuria to albuminuria. This is because microalbuminuria is considered to be a predictor of future nephropathy, especially in patients with clinical evidence of pre-diabetic insulin resistance syndrome, alternatively referred to as Syndrome X.

Accordingly, the present invention provides a compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein R^o represents 2-benzoxazolyl or 2-pyridyl and R^1 represents CH_2OCH_3 or CF_3.

Preferably, R^o represents 2-benzoxazolyl.

Suitably, R^1 represents CH_2OCH_3.

Preferably, R^1 represents CF_3.

As indicated above, a compound of formula (I), and the pharmaceutically acceptable salts thereof, may exist in one of several tautomeric forms, all of which are encompassed by the present invention as individual tautomeric forms or as mixtures thereof.

Suitable pharmaceutically acceptable salts include salts of carboxy groups and acid addition salts.

Suitable pharmaceutically acceptable salts of carboxy groups include metal salts, such as for example aluminium, alkali metal salts such as lithium, sodium or potassium, alkaline earth metal salts such as calcium or magnesium and ammonium

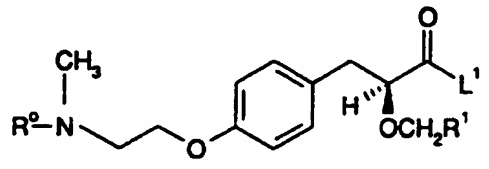
or substituted ammonium salts, for example those with lower alkylamines such as triethylamine, hydroxy alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)amine or tri-(2-hydroxyethyl)amine, cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylpiperidine, N-benzyl-β-phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine or bases of the pyridine type such as pyridine, collidine, quinine or quinoline.

Suitable acid addition salts include pharmaceutically acceptable inorganic salts such as the sulphate, nitrate, phosphate, borate, hydrochloride and hydrobromide and, where feasible, pharmaceutically acceptable organic acid addition salts such as acetate, tartrate, maleate, citrate, succinate, benzoate, ascorbate, methanesulphonate, α-keto glutarate and α-glycerophosphate.

Suitable pharmaceutically acceptable solvates include hydrates.

The salts and/or solvates of the compounds of formula (I) may be prepared and isolated according to conventional procedures, for example sodium salts may be prepared by using sodium methoxide in methanol.

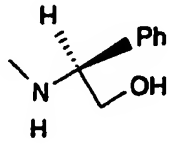
In a further aspect the present invention also provides a process for the preparation of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable hydrate thereof, which process comprises hydrolysing a compound of formula (II):



(II)

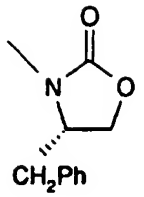
wherein R^o and R^1 are as defined in relation to formula (I) and L^1 represents a hydrolysable group; and thereafter, if required, preparing a pharmaceutically acceptable salt of the compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

A suitable hydrolysable group L^1 is a group of formula (a) or an epimer thereof:



(a)

A suitable hydrolysable group L^1 is an Evans chiral auxillary, for example a group of formula (b) or an epimer thereof:

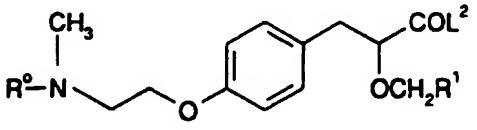


(b)

A suitable hydrolysable group L^1 is a C_{1-6} alkoxy group.

The hydrolysis of the compound of formula (II) is carried out using conditions appropriate for hydrolysing the particular group L^1 chosen, for example when L^1 is a group of formula (a) or a C_{1-6} alkoxy group, the hydrolysis is suitably carried out under acidic conditions, for example using dilute sulphuric acid, conveniently in a water/dioxan mixture, for example a 1:1 mixture, at any temperature which provides a suitable rate of formation of the required product, generally at an elevated temperature, such as in the range of from 50°C to 120°C, for example 90°C; or when L^1 is a group of formula (b) the hydrolysis is generally carried out using lithium hydroperoxide in an aqueous solvent, such as aqueous tetrahydrofuran, at any temperature which provides a suitable rate of formation of the required product, generally at a reduced temperature, such as in the range of from -10°C to 0°C, for example 0°C. Alternatively, when L^1 is a group of formula (b) the hydrolysis may be effected under basic conditions, using for example aqueous sodium hydroxide, in an appropriate solvent such as aqueous tetrahydrofuran usually at ambient temperature.

A compound of formula (II), wherein L^1 is a moiety of the above defined formula (a) or (b), may be prepared from a compound of formula (III) :



(III)

wherein R^o and R^1 are as defined in relation to formula (I) and L^2 represents a leaving group; (i) for compounds of formula (II) wherein L^1 is a moiety of the above defined formula (a), by reaction with (*S*)-phenylglycinol; or
(ii) for compounds of formula (II) wherein L^1 is a moiety of the above defined formula (b), by reaction with (*S*)-4-benzyloxazolidin-2-one, preferably an activated form thereof; and thereafter separating the required isomer from the mixture of diastereoisomers produced.

A suitable leaving group L^2 is a halogen atom, for example a chlorine atom.

The reaction between the compounds of formula (III) and (S)-phenylglycinol may be carried out under conventional amidation conditions, for example in an inert solvent such as dichloromethane at a temperature which provides a suitable rate of formation of the required product, suitably at ambient temperature and preferably in the presence of a base such as triethylamine.

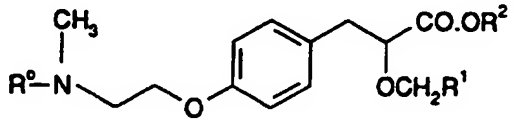
A suitable activated form of *(S)*-4-benzyloxazolidin-2-one is a salted form, for example an alkali metal salted form, preferably a lithium salt.

The activated form of *(S)*-4-benzyloxazolidin-2-one may be prepared by any appropiate conventional method. Thus when the activated form is a lithium salt, it may be prepared by treating *(S)*-4-benzyloxazolidin-2-one with a source of lithium ions in the presence of a base, suitably provided by n-butyllithium, in an aprotic solvent such as tetrahydrofuran, usually at a low temperature, for example in the range of from -78° to 0°C.

The reaction between the compound of formula (III) and the activated form of *(S)*-4-benzyloxazolidin-2-one may be carried out in an aprotic solvent, such as tetrahydrofuran, at a temperature which provides a suitable rate of formation of the required product, conveniently by allowing the reaction mixture to slowly warm from -78° to 0°C.

Preferably, the activated form of *(S)*-4-benxyloxazolidin-2-one is prepared and then reacted *in-situ* with the compound of formula (III).

A compound of formula (III) may be prepared by hydrolysing the carboxylic ester $COOR^2$ of a compound of formula (IV):



(IV)

wherein R^o and R^1 are as defined in relation to formula (I) and R^2 represents an alkyl group, and thereafter converting the carboxylic acid group so formed into a moiety $CO.L^2$.

A suitable alkyl group R^2 is a C_{1-6} alkyl group, especially a methyl group.

The hydrolysis of the carboxylic ester may be effected by use of any conventional hydrolysing agent, such as an alkaline metal hydroxide, for example sodium hydroxide.

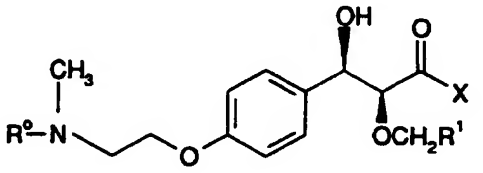
The hydrolysis of the compound of formula (IV) may be carried out in any suitable solvent such as a methanol/water mixture, conveniently a 1:1 mixture, at a temperature which provides a suitable rate of formation of the required product, suitably at an elevated temperature and conveniently at the reflux temperature of the solvent.

The conversion of the carboxylic acid group into the moiety $CO.L^2$ may be carried out using any appropiate conventional procedure, depending upon the particular nature of the group L^2 chosen, thus when L^2 is a halogen a suitable procedure involves treatment of the carboxylic acid with an oxalyl halide, for example oxalyl chloride when L^2 is chlorine.

The reaction conditions for the conversion of the carboxylic acid group into the moiety $CO.L^2$ will be dictated by the particular nature of L^2 and the source of L^2 chosen, for example when L^2 is halogen and the source of L^2 is oxalyl chloride then the reaction may be carried out in an inert solvent such as dichloromethane or benzene at a temperature which provides a suitable rate of formation of the required product, suitably at ambient temperature or at an elevated temperature such as the reflux temperature of the solvent.

It will be appreciated that the preparation and separation of a compound of formula (II) wherein L^1 is an epimer of the above defined moiety (a) or (b) and its subsequent hydrolysis to afford a compound of formula (I) can be achieved by employing analogous methods to those described above for the preparation, separation and hydrolysis of a compound of formula (II) wherein L^1 represents the above defined moiety (a) or (b).

A compound of formula (II) wherein L^1 is a moiety of formula (b) may also be prepared by dehydroxylation of a compound of formula (V):



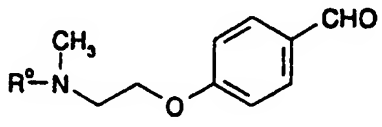
(V)

wherein R^o and R^1 are as defined in relation to formula (I) and X is a moiety of the above defined formula (b).

The dehydroxylation of the compound of formula (V) is conveniently carried out by treatment with a trialkylsilane, for example triethylsilane, preferably in the presence of trifluoroacetic acid and conveniently using trifluoroacetic acid as solvent, at any temperature providing a suitable rate of formulation of the product, for example at a temperature in the range from 0°C to room temperature.

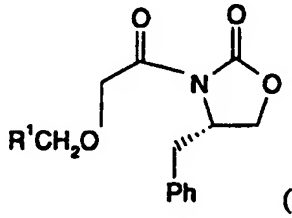
It will be appreciated that a compound of formula (II) wherein L^1 is a moiety of formula (b) would also be obtained by dehydroxylation of a compound of formula (V) in which the hydroxy bearing stereocentre is epimerised.

A compound of formula (V) may be prepared by reacting a compound of formula (VIA):



(VIA)

wherein R^O is as defined in relation to formula (I), with a compound of formula (VIB):



(VIB)

wherein R^1 is as defined in relation to formula (I); and thereafter separating the required isomer from the mixture of diastereoisomers produced.

Suitably in the above mentioned reaction, the compound of formula (VIB) is in an activated form, which is preferably provided by treating the compound of formula (VIB) with an alkylboron triflate, for example dibutylboron triflate, preferably in the presence of an amine base such as triethylamine.

The activated form of the compound of formula (VIB) may be prepared by the appropriate conventional method depending upon the specific nature of the activated form chosen, for example the compound of formula (VIB) is reacted with dibutylboron triflate and triethylamine in an inert solvent such as dichloromethane at a temperature in the range of from -78° to 0°C.

The reaction between the compounds of formulae (VIA) and (VIB) may be carried out in an in an inert solvent such as dichloromethane, at a temperature which provides a suitable rate of formation of the required product, conveniently by allowing the reaction mixture to slowly warm from -78° to 0°C.

Preferably, the activated form of the compound of formula (VIB) is prepared and then reacted *in-situ* with the compound of formula (VIA).

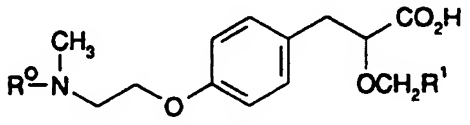
For compounds of formula (I) wherein R^O represents 2-benzoxazolyl, a suitable compound of formula (VIA) is 4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]benzaldehyde.

A suitable means for separating any required single isomer from a mixture of diastereoisomers is chromatography, such as preparative high pressure liquid chromatography or silica gel column chromatography.

One convenient method for preparing a compound of formula (II) wherein L^1 is a C_{1-6} alkoxy group is the basic alcoholysis of a compound of formula (II) wherein L^1 is a moiety of formula (b).

A suitable base is an alkali metal alkoxide, for example when L^1 is methoxy the compound of formula (II) wherein L^1 is moiety (b) is treated with sodium methoxide in methanol.

A compound of formula (I) may also be prepared by resolving a racemic compound of formula (VII):



(VII)

wherein R^o and R^1 are as defined in relation to formula (I); and thereafter, if required, preparing a pharmaceutically acceptable salt of the compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

The resolution of a compound of formula (VII) may be carried out using known resolution procedures, for example by reacting the compound of formula (VII) with a resolving agent, such as an optically active acid or base, to provide a mixture of diastereoisomeric salts which may then be separated by fractional crystallisation and thereafter the compound of formula (I) may be regenerated from the separated diastereoisomer salt by conventional means, such as hydrolysis.

It will be appreciated that the compounds of formula (VII) comprise the compounds of formula (I) admixed with other optical isomers. A compound of formula (VII) or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, forms a further aspect of the present invention. The separated isomers of the compounds of formula (VII), in addition to the compounds of formula (I), or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, also comprise the present invention.

Suitable acids or bases for resolving the compounds of formula (VII) are as described in Enantiomers, Racemates and Resolution, J Jaques et al, 1981, Wiley Interscience, especially at pages 255 and 256. Suitable methods for effecting the resolution are also disclosed by Jaques et al.

The compounds of formula (II) and (III) form a further aspect of the present invention.

The compounds of formula (IV) and (VIA), for example 4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]benzaldehyde, are known compounds or they may be prepared using methods analogous to those used to prepare known compounds, for example th se disclosed in International Patent Application, Publication Number WO94/01420.

The compounds of formula (VIB) are known compounds or they may be prepared using methods analogous to those used to prepare known compounds, for example those disclosed in Organic Synthesis Vol. 68, p83, 1990 Ed. J.D. White or methods analogous thereto, in combination with conventional methodology for the preparation of acid chlorides.

It will be appreciated that in any of the abovementioned reactions any reactive group in the substrate molecule may be protected, according to conventional chemical practice. Suitable protecting groups in any of the abovementioned reactions are those used conventionally in the art. The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected.

It will be appreciated that the above mentioned preparation of the compounds of formula (I), or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, is a stereoselective procedure and that the compound of formula (I) is a single stereoisomer. The present invention also includes a compound of formula (I) when present in admixture with less than 50% w/w of its racemic isomer, that is when it is greater than 50% optically pure, suitably 80-100% and preferably 90-100% pure, such as 90-95%, most preferably 95-100%, for example 95%, 96%, 97%, 98%, 99% or 99.9% optically pure.

In one preferred aspect there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, in optically pure form.

The absolute stereochemistry of compounds may be determined using conventional methods, such as X-ray crystallography.

As mentioned above the compounds of the invention are indicated as having useful therapeutic properties: The present invention accordingly provides a compound of formula (I), or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use as an active therapeutic substance.

Thus the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment of and/or prophylaxis of hyperglycaemia.

In a further aspect the present invention also provides a compound of formula (I), or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment and/or prophylaxis of hyperlipidaemia.

As indicated hereinbefore the present invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof f r use in the treatment of hypertension, cardiovascular disease, certain eating disorders and/or the treatment and/or prophylaxis of renal disease.

In addition, the present invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the prevention, reversal, stabilisation or retardation of the progression of microalbuminuria to albuminuria.

Cardiovascular disease includes in particular atherosclerosis.

Certain eating disorders include in particular the regulation of appetite and food intake in subjects suffering from disorders associated with under-eating ,such as anorexia nervosa, and disorders associated with over-eating, such as obesity and anorexia bulimia.

Renal disease includes renal disease associated with the development of Type II diabetes including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

A compound of formula (I), or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier.

Accordingly, the present invention also provides a pharmaceutical composition comprising a compound of the general formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier therefor.

As used herein the term 'pharmaceutically acceptable' embraces compounds, compositions and ingredients for both human and veterinary use: for example the term 'pharmaceutically acceptable salt' embraces a veterinarily acceptable salt.

The composition may, if desired, be in the form of a pack accompanied by written or printed instructions for use.

Usually the pharmaceutical compositions of the present invention will be adapted for oral administration, although compositions for administration by other routes, such as by injection and percutaneous absorption are also envisaged.

Particularly suitable compositions for oral administration are unit dosage forms such as tablets and capsules. Other fixed unit dosage forms, such as powders presented in sachets, may also be used.

In accordance with conventional pharmaceutical practice the carrier may comprise a diluent, filler, disintegrant, wetting agent, lubricant, colourant, flavourant or other conventional adjuvant.

Typical carriers include, for example, microcrystalline cellulose, starch, sodium starch glycollate, polyvinylpyrrolidone, polyvinylpolypyrrolidone, magnesium stearate or sodium lauryl sulphate.

Most suitably the composition will be formulated in unit dose form. Such unit dose will normally contain an amount of the active ingredient in th range of from 0.1 to 1000 mg, more usually 0.1 to 500 mg, and more especially 0.1 to 250 mg.

The present invention further provides a method for the treatment and/or prophylaxis of hyperglycaemia in a human or non-human mammal which comprises administering an effective, non-toxic, amount of a compound of the general formula (I), or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof to a hyperglycaemic human or non-human mammal in need thereof.

The present invention further provides a method for the treatment of hyperlipidaemia, hypertension, cardiovascular disease, certain eating disorders, the treatment and/or prophylaxis of renal disease and/or the prevention, reversal, stabilisation or retardation of the progression of microalbuminuria to albuminuria in a human or non-human mammal, which comprises administering an effective, non-toxic, amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, to a human or non-human mammal in need thereof.

Conveniently, the active ingredient may be administered as a pharmaceutical composition hereinbefore defined, and this forms a particular aspect of the present invention.

In the treatment and/or prophylaxis of hyperglycaemic humans, and/or the treatment and/or prophylaxis of hyperlipidaemic human, the compound of the general formula (I), or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may be taken in doses, such as those described above, one to six times a day in a manner such that the total daily dose for a 70 kg adult will generally be in the range of from 0.1 to 6000 mg, and more usually about 1 to 1500 mg.

In the treatment and/or prophylaxis of hyperglycaemic non-human mammals, especially dogs, the active ingredient may be adminstered by mouth, usually once or twice a day and in an amount in the range of from about 0.025 mg/kg to 25 mg/kg, for example 0.1 mg/kg to 20 mg/kg. Similar dosage regimens are suitable for the treatment and/or prophylaxis of hyperlipidaemia in non-human mammals.

The dosages regimens for the treatment of hypertension, cardiovascular disease and eating disorders hypertension, cardiovascular disease, certain eating disorders, the treatment and/or prophylaxis of renal disease and/or the prevention, reversal, stabilisation or retardation of the progression of microalbuminuria to albuminuria will generally be those mentioned above in relation to hyperglycaemia.

In a further aspect the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof and/or a pharmaceutically

acceptable solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of hyperglycaemia.

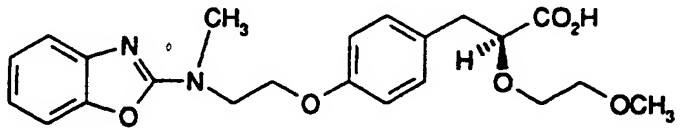
The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of hyperlipidaemia, hypertension, cardiovascular disease or certain eating disorders and/or the prophylaxis of renal disease and/or in the prevention, reversal, stabilisation or retardation of the progression of microalbuminuria to albuminuria.

No toxicological effects have been established for a compound of formula (I) or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, in the abovementioned dosage ranges.

The following Procedures and Examples illustrate the invention but do not limit it in any way.

Example 1

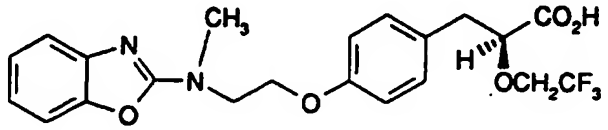
***(S)*-3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-methoxyeth xy)propan ic acid**



A solution of [2S, N(1S)]-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]-phenyl]-2-(2-methoxyethoxy)-N-(2-hydroxy-1-phenylethyl)propanamide (1.846 g) in a mixture of 1M sulphuric acid (45 mL) and dioxan/water (1:1, 150 mL) was heated at 90°C for 56 hours and then the pH of the mixture was adjusted to pH 3 by addition of aqueous sodium hydrogen carbonate. The mixture was extracted with ethyl acetate and the organic extracts washed with water, brine, dried ($MgSO_4$) and evaporated to give an oil. Purification by chromatography on silica gel using a gradient of 1-5% methanol in dichloromethane as eluent gave a foam of 88% e.e. (by HPLC). The product was reacted with *(S)*-α-methylbenzylamine in acetone, and the resulting salt recrystallised several times from ethyl acetate-hexane before being dissolved in water, acidified with dilute hydrochloric acid and extracted with ethyl acetate which was dried with $MgSO_4$. Evaporation of the ethyl acetate solution afforded enantiomerically enriched title compound; $[\alpha]_D^{25}$ –28° (c=0.625, $CHCl_3$); e.e 94% (by HPLC); [Found M^+ 414.1791. $C_{22}H_{26}N_2O_6$ requires M^+ 414.1791]; ^1H NMR spectrum identical with that described in Example 5.

Example 2

***(S)*-3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoic acid by hydrolysis of amide**

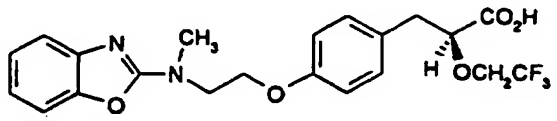


[2S, N(1S)]-3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)-N-(2-hydroxy-1-phenylethyl)propanamide (from Procedure 3) was hydrolysed by an analogous procedure to that described in Example 1. Purification by chromatography on silica gel using a gradient of 0-5% methanol in dichloromethane as eluent gave the title compound, mp 116-7°C, after trituration with diethyl ether-hexane; $[\alpha]_D^{25}$ -24.6° (c=0.24, $CHCl_3$); e.e. 95% (by HPLC). [Found C, 57.9; H, 4.7; N, 6.8%; M^+ 438.1403. $C_{21}H_{21}F_3N_2O_5$ requires C, 57.5; H,

4.8; N, 6.4%; M^+ 438.1403]; δ_H (DMSO-d_6) 2.96 (2H,m), 3.22 (3H,s), 3.88 (2H,m), 3.95-4.18 (2H,m), 4.27 (3H,m), 6.8-7.37 (8H,m) and 12.9 (1H,br s, exchanges with D_2O).

Example 3

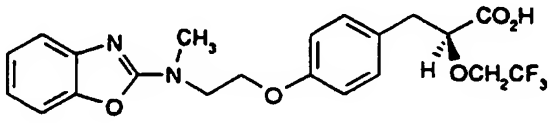
***(S)*-3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl-2-(2,2,2-trifluoroethoxy)propanoic Acid, by Direct Hydrolysis of the Imide**



Aqueous sodium hydroxide solution (2.5M, 65 mL, 0.163 mol, 2.3 eq) was added to a stirred solution of [3(2*S*), 4*S*]-3-[3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoyl]-4-benzyloxazolidin-2-one (from Procedure 10)(42.5 g, 0.071 mol) in THF (500 mL) and water (125 mL). The mixture was stirred for 20 minutes, the reaction was diluted with water (1 L) and extracted with dichloromethane (3 x 700 mL). These dichloromethane solutions were evaporated and the residue purified by chromatography on silica gel using 5% methanol in dichloromethane as eluent to afford *(S)*-4-benzyloxazolidin-2-one. The original aqueous solution was acidified to pH 3.5 with dilute hydrochloric acid and re-extracted with dichloromethane (3 x 700 mL). The dichloromethane solutions from the acid extraction were dried ($MgSO_4$) and evaporated to give a solid. This was recrystallised from dichloromethane-diethyl ether to afford the title compound, mp 119.5-120.5°C. $[\alpha]_D^{25} = -31°$ (c = 2.50, $CHCl_3$); e.e. 99.6% (by HPLC); [Found C, 57.7; H, 4.7; N, 6.25%; M^+ (EI) 438.1412. $C_{21}H_{21}F_3N_2O_5$ requires C, 57.5; H, 4.8; N, 6.4%; M^+ 438.1403]; δ_H ($CDCl_3$) 3.05 (1H, dd), 3.13 (1H, dd), 3.31 (3H, s), 3.72 (1H, m), 3.89 (2H, m), 4.04-4.14 (3H, m), 4.21 (1H, dd), 6.78 (2H, d), 7.03-7.40 (6H, m) and 11.20 (1H, br, exchanges with D_2O); δ_F (DMSO-d_6) = -72.7 (3F, t, $^3J_{HF}$ 9.3 Hz, CF_3).

Example 4

***(S)*-3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl-2-(2,2,2-trifluoroethoxy)propanoic Acid by Hydrolysis of Methyl Ester**

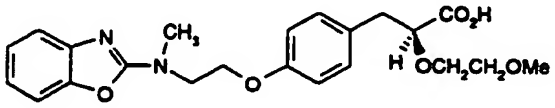


A mixture of *(S)*-methyl 3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoate (1.256 g, 2.8 x 10^{-3}

mol), aqueous hydrochloric acid (2.0M, 50 mL) and dioxan (50 mL) was heated at reflux for 7 hours, cooled and concentrated *in vacuo*. The residue was suspended in brine (200 mL) and extracted with ethyl acetate (3 x 300 mL). The combined ethyl acetate solutions were dried ($MgSO_4$) and evaporated to afford a waxy solid. This solid was triturated with hexane, filtered and dried under vacuum at 65°C to afford the desired product, mp 113-5°C. $[\alpha]_D^{25}$ = -32° (c = 1.02, $CHCl_3$); e.e. 99.4% (by HPLC); [Found C, 57.25; H, 4.8; N, 6.3%. $C_{21}H_{21}F_3N_2O_5$ requires C, 57.5; H, 4.8; N, 6.4%]. The ^1H NMR spectrum of this material was identical to that produced in Example 3.

Example 5

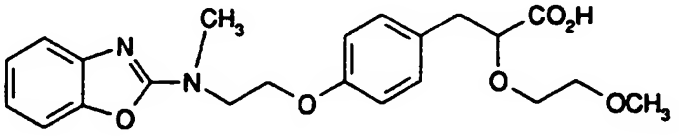
***(S)*-3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl-2-(2-methoxyethoxy)propanoic Acid**



(S)-Methyl 3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-methoxyethoxy)propanoate was hydrolysed in a manner analogous to that described for Example 4. The crude reaction mixture was chromatographed on silica gel using 5% methanol in dichloromethane as eluent to afford the title compound, a gum. $[\alpha]_D^{25}$ = -27° (c = 0.73, $CHCl_3$); e.e. 99.8% (by HPLC); [Found M^+ (EI) 414.1779. $C_{22}H_{26}N_2O_6$ requires M^+ 414.1791]; δ_H ($CDCl_3$) 2.90 (1H, dd), 3.15 (1H, dd), 3.33 (3H, s), 3.37 (3H, s), 3.40-3.70 (4H, m), 3.93 (2H, t), 4.05 (1H, dd), 4.21 (2H, t), 6.81 (2H, d) and 6.95-7.40 (6H,m).

Procedure 1

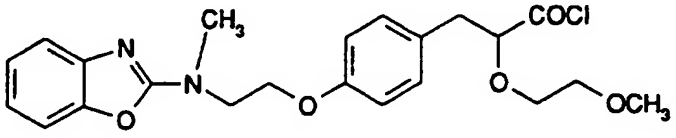
(±)-3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-methoxyethoxy]propanoic acid



A mixture of methyl 3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-methoxyethoxy)propanoate (1.08 g, *Int. Patent Appl., Publication No.* WO 9401420) and sodium hydroxide (253 mg) in methanol:water (1:1, 10 mL) was heated under reflux for 2 hours. After evaporation of the resultant mixture *in vacuo*, the residue was diluted with water, acidified to pH 5 with 2M hydrochloric acid and then extracted with ethyl acetate. Washing of the ethyl acetate extracts with water and drying ($MgSO_4$) and evaporation gave the title compound as an oil which crystallised on trituration with diethyl ether/hexane. [Found C, 63.8; H, 6.5; N, 7.0%; M^+ 414.1791. $C_{22}H_{26}N_2O_6$ requires C, 63.8; H, 6.3; N, 6.8%; M^+ 414.1791]; δ_H ($CDCl_3$) 2.91 (1H,dd), 3.15 (1H,dd), 3.34 (3H,s), 3.38 (3H,s), 3.41-3.69 (4H,m), 3.93 (2H,t), 4.05 (1H,dd), 4.21 (2H,t), 6.80 (2H,d) and 6.83-7.38 (6H m).

Procedure 2

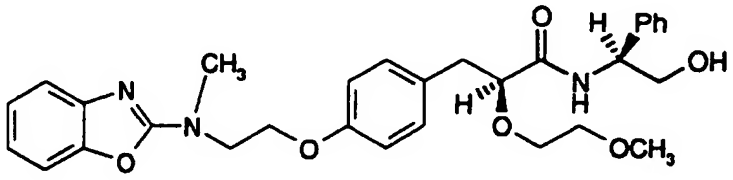
(±)-3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-methoxyethoxy)propanoyl chloride



Oxalyl chloride (92 mg) was added to (±)-3-[4-[2-[N-(2-benzoxazolyl)-N-methyl-amino]ethoxy]phenyl]-2-(2-methoxyethoxy)propanoic acid (100 mg) in dichloromethane (2 mL). The mixture was stirred at room temperature for 16 hours and evaporated to dryness to give the title compound as a gum which was used without further purification.

Procedure 3

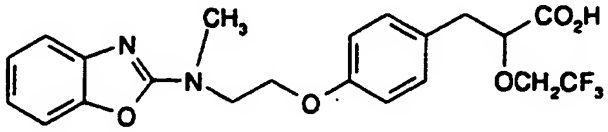
[2*S*, N(1*S*)]-3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]eth xy]phenyl]-2-(2-methoxyethoxy)-N-(2-hydroxy-1-phenylethyl)pr panamide



(±)-3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-methoxyethoxy)propanoyl chloride was dissolved in dichloromethane (2 mL) and a mixture of *(S)*-2-phenylglycinol (33 mg) and dry triethylamine (37 mg) in dichloromethane (1 mL) added. After stirring for 5 minutes water was added and the mixture extracted with dichloromethane. The organic extracts were washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel using a gradient of 10-50% acetone in hexane as eluent to afford firstly [2*R*, N(1*S*)]-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-methoxyethoxy)-N-(2-hydroxy-1-phenylethyl)propanamide followed by the desired [2*S*, N(1*S*)]-propanamide title compound as a foam. $[\alpha]_D^{25}$ –33° (c=1.1, $CHCl_3$); 92.6% d.e. (by HPLC); [Found M^+ 533.2526. $C_{30}H_{35}N_3O_5$ requires M^+ 533.2526]; δ_H ($CDCl_3$) 2.81 (1H,dd), 3.07 (1H,dd), 3.35 (3H,s), 3.36 (3H,s), 3.48-3.58 (2H,m), 3.52-3.62 (2H,m), 3.71 (1H,dd), 3.82 (1H,dd), 3.94 (1H,dd), 3.93 (2H,t), 4.22 (3H,t), 5.05 (1H,dt), 6.75-7.35 (13H,complex), 7.54 (1H,br, exchanges with D_2O).

Procedure 4

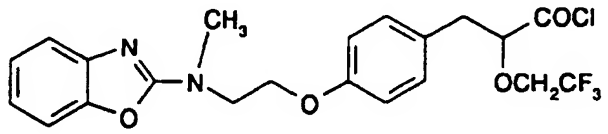
(±)-3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoic acid



Methyl 3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoate (*Int. Patent Appl., Publication No.* WO 9401420) was hydrolysed by an analogous procedure to that described in Procedure 1 to give the title compound as a solid, mp 116-117°C; [Found C, 57.4; H, 4.9; N, 6.4%. $C_{21}H_{21}F_3N_2O_5$ requires C, 57.5; H, 4.8; N, 6.4%]; δ_H ($CDCl_3$) 3.03-3.17 (2H,m), 3.29 (3H,s), 3.73-3.83 (1H,m), 3.85 (2H,m), 4.02 (2H,m), 4.04-4.30 (2H,m) and 6.74-7.40 (8H m).

Procedure 5

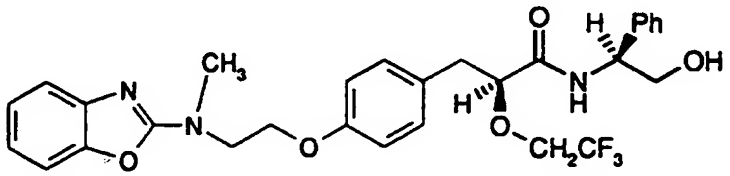
(±)-3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-triflu roethoxy)propanoyl chloride



Oxalyl chloride (1.1 mL) was added to a solution of (±)-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoic acid (1.72 g) in dry benzene (30 mL). The mixture was heated at reflux for 2 hours, cooled and evaporated to dryness to give the title compound as a gum which was used without further purification.

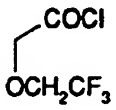
Procedure 6

[2S, N(1S)]-3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)-N-(2-hydroxy-1-phenylethyl)propanamide



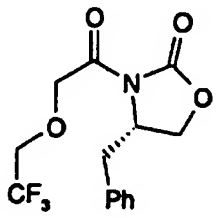
(±)-3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoyl chloride was reacted with *(S)*-2-phenylglycinol by an analogous procedure to that described in Procedure 3. Chromatography on silica gel using a gradient of 10-70% ethyl acetate in hexane as eluent afforded firstly [2*R*, N(1*S*)]-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)-N-(2-hydroxy-1-phenylethyl)propanamide followed by the desired [2*S*, N(1*S*)]-propanamide title compound as a foam; $[\alpha]_D^{25}$ +14° (c=0.5, MeOH); 99% d.e. (by HPLC); [Found M^+ 557.2136. $C_{29}H_{30}F_3N_3O_5$ requires M^+ 557.2138]; δ_H ($CDCl_3$) 2.35 (1H,br, exchanges with D_2O), 2.91 (1H,dd), 3.13 (1H,dd), 3.36 (3H,s), 3.70-3.87 (2H,m), 3.84 (2H,d), 3.95 (2H,t), 4.12 (1H,dd),4.22 (2H,t), 5.01 (1H,m), 6.75 (2H,d), 6.97 (1H,br s, exchanges with D_2O) and 7.01-7.36 (11H,complex).

Procedure 7
(2,2,2-Trifluoroethoxy)ethanoyl Chl ride



A solution of oxalyl chloride (20 mL, 0.23 mol, 1.15 eq) in dry dichloromethane (50 mL) was added dropwise at room temperature, with stirring, to a solution of (2,2,2-trifluoroethoxy)ethanoic acid (*Int. Patent Appl., Publication No.* WO 87/07270, 31.6 g, 0.2 mol) and N,N-dimethylformamide (5 drops) in dry dichloromethane (400 mL). The mixture was stirred for an additional hour, then heated under reflux for 2 hours, cooled and the bulk of the solvent removed by distillation (bp 40-45°C/760 mm Hg). The residue was transferred to a Claisen distillation flask and the remaining solvent and oxalyl chloride removed by distillation (bp 45-60°C/760 mm Hg). Vacuum distillation of the residue then afforded the product, bp 50-55°/25-32 mm Hg. δ_H ($CDCl_3$) 4.00 (2H, q, $^3J_{HF}$ 8.3) and 4.57 (2H, s).

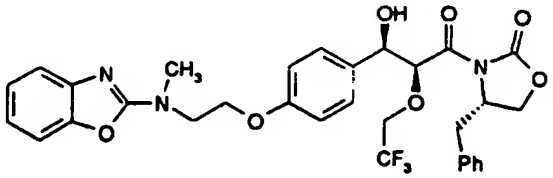
Procedure 8
(4*S*)-4-Benzyl-3-[2-(2,2,2-trifluoroethoxy)ethanoyl]oxazolidin-2-one



(4*S*)-4-Benzyloxazolidine-2-one (5.21 g, 0.029 mol) was dissolved in dry THF (60 mL) and cooled to -70°C under argon. *n*-Butyllithium (18.4 mL, 1.6 M solution in hexane, 1.1 eq) was added over 10 minutes and the resulting mixture stirred at -70° C for 20 minutes. A solution of (2,2,2-trifluoroethoxy)ethanoyl chloride (5.19 g, 1 eq) in dry THF (60 mL) was added over 10 minutes, the mixture stirred at -70°C for a further 30 minutes then allowed to warm to room temperature overnight. The reaction was quenched by addition of brine (20 mL) and concentrated *in vacuo*. The residue was diluted with brine (300 mL) and extracted with ethyl acetate (3 x 300 mL). The combined organic extracts were dried ($MgSO_4$), evaporated and the residue chromatographed on silica gel with dichloromethane as eluent to give the product as an oil. $[\alpha]_D^{25}$ = +48° (c = 2.55, $CHCl_3$); e.e. 100% (by HPLC); [Found (CI, Ammonia) MH^+ 318.0934. $C_{14}H_{14}NO_4F_3$ requires MH^+ 318.0953]; δ_H ($CDCl_3$) 2.82 (1H, dd), 3.34 (1H, dd), 4.02 (2H, q, $^3J_{HF}$ 8.6), 4.30 (2H, m), 4.69 (1H, m), 4.84 (2H, s) and 7.15-7.40 (5H, m); δ_F ($CDCl_3$) = -74.8 (3F, t, $^3J_{HF}$ 8.6, CF_3).

Procedure 9

[3(2*S*, 3*R*), 4*S*]-3-[3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-3-hydroxy-2-(2,2,2-trifluoroethoxy)propanoyl]-4-benzyloxazolidin-2-one

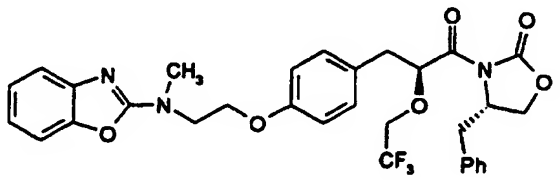


(4*S*)-4-Benzyl-3-[2-(2,2,2-trifluoroethoxy)ethanoyl]oxazolidin-2-one (31.7 g, 0.1 mol) was dissolved in dry dichloromethane (300 mL) under argon and cooled to -78°C (internal temperature of solution), using liquid nitrogen/acetone as the cooling medium. Triethylamine (16.72 mL, 1.2 eq) was added, followed by the slow addition, over approximately 10 minutes, of di-*n*-butylboron triflate (Aldrich Chemical Company, 1.0M solution in dichloromethane, 110 mL, 1.1 eq) such that the reaction temperature was maintained below -70°C. The mixture was stirred at -78°C for 50 minutes, then the cooling bath was replaced with an ice bath and the mixture stirred at 0°C for an additional 50 minutes before being recooled to -78°C. A solution of 4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]benzaldehyde (29.6 g, 1.0 eq) in dry dichloromethane (220 mL), precooled to -50°C, was added over *ca.* 12 minutes, such that the reaction temperature was maintained below -70°C. The resulting mixture was stirred at -78°C for 30 minutes, then warmed from -78°C to 0°C over 60 minutes along a linear gradient (warming rate ~ 1.3°C.min^{-1}) and stirred at 0°C for a further 75 minutes. The reaction mixture was poured into a quenching solution of methanol (500 mL), pH 7 phosphate buffer (250 mL) and hydrogen peroxide (27.5% w/v, 110 mL) and stirred vigourously for 30 minutes. Water (4 L) was added, the layers were separated and the aqueous layer was extracted with dichloromethane (3 x 1 L). The dichloromethane solutions were recombined with the original dichloromethane layer from the reaction mixture and this organic solution was then washed with water (2 L) and brine (2 L), dried ($MgSO_4$) and evaporated to afford a foam. ^{1}H NMR of this crude reaction mixture suggested a mixture of the desired aldol product (3 diastereoisomers, comprising 95% major diastereoisomer) and starting materials. The crude mixture was chromatographed on silica gel using a gradient elution comprising 15% ethyl acetate in dichloromethane initially (until the desired product began to elute) and rising to 50% ethyl acetate in dichloromethane to complete the elution of the desired product. Unreacted imide and aldehyde were recovered from the early fractions, followed by a quantity of impure product and then the title compound (comprising 2 diastereoisomers, ratio 97.8:2.2 by NMR). $[\alpha]_D^{25}$

= +45° (c = 2.82, $CHCl_3$). [Found (EI) M^+ 613.2042. $C_{31}H_{30}F_3N_3O_7$ requires M^+ 613.2036]; δ_H ($CDCl_3$, only major diastereoisomer is recorded) 2.75 (1H, dd), 2.90 (1H, d, exchanges with D_2O), 3.25 (1H, dd), 3.34 (3H, s), 3.80-4.00 (5H, m), 4.07 (1H, dd), 4.24 (2H, t), 4.45 (1H, m), 4.99 (1H, apparent t), 5.48 (1H, d), 6.85 (2H, d) and 6.95-7.40 (11H, m); δ_F ($CDCl_3$) = -74.7 (3F, t, $^3J_{HF}$ 8.5, CF_3). The minor diastereoisomer in the purified product was identified as the [3(2*S*, 3*S*), 4*S*]-diastereoisomer.

Procedure 10

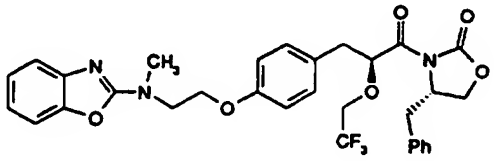
Preparation of [3(2*S*), 4*S*]-3-[3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoyl]-4-benzyloxazolidin-2-one by Dehydroxylation



Triethylsilane (120 mL, 0.75 mol) was added over 5 minutes to a stirred, ice cooled solution of [3(2*S*, 3*R*), 4*S*]-3-[3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-3-hydroxy-2-(2,2,2-trifluoroethoxy)propanoyl]-4-benzyloxazolidin-2-one (46.23 g, 7.5 x 10^{-2} mol) in trifluoroacetic acid (650 mL). The mixture was stirred at 0°C for 1 hour, then at room temperature for a further 60 hours. The bulk of the solvent and residual triethylsilane was removed by rotary evaporation, firstly at 40 mm Hg and finally at ~5 mm Hg. The residue was dissolved in dichloromethane (800 mL) and water (800 mL), then stirred vigorously during the cautious addition of solid sodium bicarbonate (~29 g) (frothing !) until the pH of the aqueous layer was pH 7. The layers were separated and the aqueous layer was extracted with dichloromethane (800 mL). The combined dichloromethane layers were washed with water (600 mL), dried ($MgSO_4$) and evaporated. The residue was triturated with hot hexane and the resulting solid collected by filtration. Recrystallisation from diethyl ether-hexane afforded the title compound, mp 107-109°C, a single diastereoisomer by ^1H NMR spectroscopy. $[\alpha]_D^{25}$ = +38° (c = 1.51, $CHCl_3$); [Found C, 62.1; H, 4.9; N, 7.2%; M^+ (EI) 597.2089. $C_{31}H_{30}N_3O_6F_3$ requires C, 62.3; H, 5.1; N, 7.0%; M^+ 597.2087]; δ_H ($CDCl_3$) 2.82 (1H, dd), 2.96 (1H, dd), 3.04 (1H, dd), 3.32 (1H, dd), 3.34 (3H, s), 3.70 (1H, m), 3.88 (1H, m), 3.94 (2H, t), 4.12 (1H, m), 4.18 (1H, m), 4.25 (2H, t), 4.57 (1H, m), 5.34 (1H, dd), 6.82 (2H, d) and 7.00-7.35 (11H, m); δ_F ($CDCl_3$) = -74.8 (3F, t, $^3J_{HF}$ 8.6, CF_3).

Procedure 11

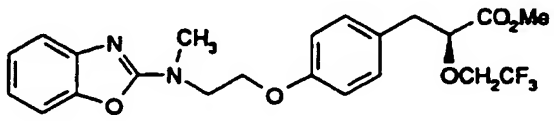
Preparation f [3(2*S*), 4*S*]-3-[3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]-eth xy]phenyl]-2-(2,2,2-trifluoroethoxy)propan yl]-4-benzyloxazolidin-2-one by Diastereoisomer Separation



(S)-4-Benzyloxazolidin-2-one (0.291 g, 1.64 x 10^{-3} mol) was dissolved in dry THF (10 mL) and the resulting solution cooled to -70°C under argon. *n*-Butyl lithium (1.6M in hexane, 1.03 mL, 1.64 x 10^{-3} mol) was added and the mixture was stirred at -70°C for 10 minutes prior to the addition of a solution of (±)-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoyl chloride (prepared from 0.36 g of the acid by Procedure 5, above) in dry THF (15 mL). The reaction was stirred and allowed to warm to room temperature overnight before being diluted with water (200 mL) and extracted with ethyl acetate (2 x 200 mL). The combined ethyl acetate layers were washed with water (200 mL) and brine (200 mL), dried ($MgSO_4$) and evaporated to give a brown gum. This was chromatographed on silica gel using a gradient of 35% to 50% ethyl acetate in hexane as eluent to afford firstly the *(R, S)*-diastereoisomer, followed by the title compound, a foam. This material was spectroscopically identical with that prepared by the aldol route (Procedure 10).

Procedure 12

***(S)*-Methyl 3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoate**

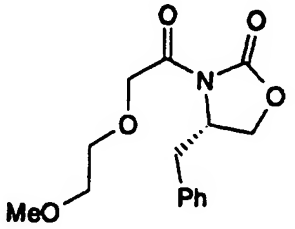


A solution of sodium methoxide [prepared from sodium hydride (60% dispersion in mineral oil, 138 mg, 3.41 x 10^{-3} mol) dissolved in dry methanol (3.5 mL)] was added to an ice cooled and stirred suspension of [3(2*S*), 4*S*]-3-[3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoyl]-4-benzyloxazolidin-2-one (1.879 g, 3.1 x 10^{-3} mol) in dry methanol (100 mL). The mixture was stirred at 0°C for a total of 20 minutes, then the reaction was quenched by the addition of dilute aqueous hydrochloric acid (2.0M, 1.75 mL) and c ncentrated *in vacuo*. The residue was suspended in water (100 mL), extracted with ethyl acetate

(3 x 200 mL) and the combined ethyl acetate solutions washed with brine (500 mL), dried ($MgSO_4$) and evaporated. The resulting gum was chromatographed on silica gel using 4% ethyl acetate in dichloromethane as eluent to afford the product as a clear gum. $[\alpha]_D^{25} = -17°$ (c = 1.24, $CHCl_3$); [Found (EI) M^+ 452.1561. $C_{22}H_{23}N_2O_5F_3$ requires M^+ 452.1559]; e.e. 100% (by HPLC); δ_H ($CDCl_3$) 3.02 (2H, m), 3.34 (3H, s), 3.65 (1H, m), 3.72 (3H, s), 3.94 (2H, t), 4.00 (1H, m), 4.13 (1H, dd), 4.24 (2H, t), 6.80 (2H, d) and 6.96-7.40 (6H, m).

Procedure 13

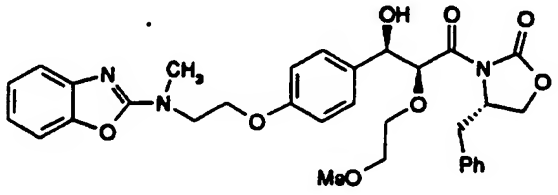
(4*S*)-4-Benzyl-3-[2-(2-methoxyethoxy)ethanoyl]oxazolidin-2-one



The title compound was prepared from 2-(2-methoxyethoxy)ethanoyl chloride by a method analogous to that described in Procedure 8. Chromatography on silica gel using a gradient of 70-80% diethyl ether in hexane as eluent afforded the product as a gum. $[\alpha]_D^{25} = +54°$ (c = 2.70, $CHCl_3$); [Found (EI) M^+ 293.1263. $C_{15}H_{19}NO_5$ requires M^+ 293.1264]; δ_H ($CDCl_3$) 2.81 (1H, dd), 3.33 (1H, dd), 3.41 (3H, s), 3.63 (2H, t), 3.78 (2H, t), 4.25 (2H, m), 4.70 (1H, m), 4.74 (1H, d), 4.76 (1H, d) and 7.10-7.40 (5H, m).

Procedure 14

[3(2*S*, 3*R*), 4*S*]-3-[3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-3-hydroxy-2-(2-methoxyethoxy)propanoyl]-4-benzyloxazolidin-2-one

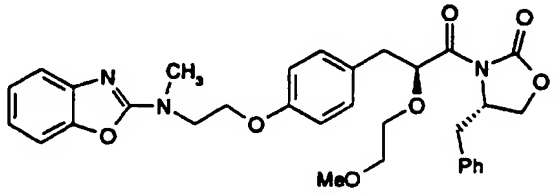


The title compound was prepared from (4*S*)-4-benzyl-3-[2-(2-methoxyethoxy)ethanoyl]oxazolidin-2-one by a method analogous to that described in Procedure 9. The crude reaction mixture was chromatographed on silica gel using a gradient of 15-40% ethyl acetate in dichloromethane t afford the product as a gum (comprising 2 diastereoisomers, ratio >99:1 by ^1H NMR). $[\alpha]_D^{25} = +49°$ (c = 1.14, $CHCl_3$). [Found (FAB, NOBA/Na) MH^+ 590.2472. $C_{32}H_{35}N_3O_8$ requires MH^+

590.2502]; δ_H ($CDCl_3$, only major diastereoisomer is recorded) 2.71 (1H, dd), 3.25 (1H, dd), 3.31 (3H, s), 3.35 (3H, s), 3.56 (2H, m), 3.72 (2H, m), 3.78 (1H, d, exchanges with D_2O), 3.85-4.00 (4H, m), 4.22 (2H, t), 4.31 (1H, m), 4.89 (1H, dd), 5.42 (1H, d), 6.83 (2H, d) and 6.95-7.40 (11H, m); The minor diastereoisomer in the purified product was identified as the [3(2*S*, 3*S*), 4*S*]-diastereoisomer.

Procedure 15

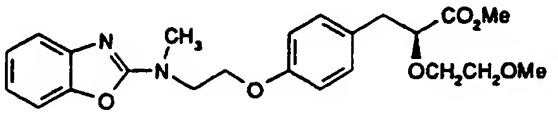
[3(2*S*), 4*S*]-3-[3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-methoxyethoxy)propanoyl]-4-benzyloxazolidin-2-one



[3(2*S*, 3*R*), 4*S*]-3-[3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-3-hydroxy-2-(2-methoxyethoxy)propanoyl]-4-benzyloxazolidin-2-one (0.561g) was reacted with triethylsilane for 6.25 hrs in a manner similar to that described for Procedure 10. The reaction mixture was diluted with water (200 mL) and dichloromethane (200 mL) and solid sodium bicarbonate was added cautiously until the aqueous layer showed pH 6.5. The layers were separated, the aqueous layer was extracted with dichloromethane (2 x 300 mL) and the combined dichloromethane solutions were washed with brine (400 mL), dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel using 35% ethyl acetate in dichloromethane as eluent to afford the title compound, a gum, as a single diastereoisomer by ^1H NMR. $[\alpha]_D^{25}$ = +45° (c = 1.39, $CHCl_3$); [Found M^+ (EI) 573.2473. $C_{32}H_{35}N_3O_7$ requires M^+ 573.2475]; δ_H ($CDCl_3$) 2.76 (1H, dd), 2.94 (2H, m), 3.30 (3H, s), 3.33 (4H, m), 3.40-3.70 (4H, m), 3.93 (2H, t), 4.00 (1H, dd), 4.12 (1H, dd), 4.22 (2H, t), 4.52 (1H, m), 5.31 (1H, dd), 6.79 (2H, d) and 6.90-7.40 (11H, m).

Procedure 16

***(S)*-Methyl 3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-methoxyethoxy)propanoate**



[3(2*S*), 4*S*]-3-[3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-methoxyethoxy)propanoyl]-4-benzyloxazolidin-2-one was reacted with sodium methoxide in a manner analogous to that described in Procedure 12. The crude reaction mixture was chromatographed on silica gel using 20% isohexane in diethyl ether as eluent to afford the title compound, a gum. $[\alpha]_D^{25} = -12°$ (c = 1.26, $CHCl_3$); [Found (EI) M^+ 428.1974. $C_{23}H_{28}N_2O_6$ requires M^+ 428.1948]; e.e. >99.8% (by HPLC); δ_H ($CDCl_3$) 2.95 (2H, m), 3.29 (3H, s), 3.34 (3H, s), 3.35 (3H, m), 3.69 (4H, m), 3.93 (2H, t), 4.05 (1H, dd), 4.23 (2H, t) and 6.75-7.40 (8H, m).

DEMONSTRATION OF EFFICACY OF COMPOUNDS

Obese Mice, Oral Glucose T lerance Test.

C57bl1/6 obese (ob/ob) mice were fed on powdered oxoid diet. After at least one week, the mice continued on a powdered oxoid diet or were fed powered oxoid diet containing the test compound. After 8 days on the supplemented diet all of the mice were fasted for 5 hours prior to receiving an oral load of glucose (3g/kg). Blood samples for glucose analysis were taken 0, 45, 90 and 135 minutes after glucose administration and the results appear below as the percentage reduction in area under the blood glucose curve where test compound treated groups are compared with the control group. 8 mice were used for each treatment.

Table

Example	Level in diet (μmol. kg^{-1} of diet)	% Reduction in area under blood glucose curve
1	0.3	24
2	0.3	24

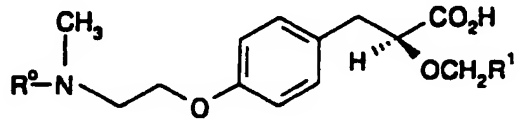
Effects on packed red cell volume and heart weight:

These were determined after repeat oral administration of compound (once daily at a dose of 3 µmol/kg body wt for 14 days, by gavage) to female Sprague- Dawley rats for 14 days. Changes shown are percentage changes from control. Statistical comparisons were made by Student t test for non-paired data; *$p<0.05$, ***$p<0.001$ versus controls. No effect no significant difference from control group. Results were obtained from 8 rats per treatment group.

Example	Compound Heart weight (% increase)	Packed cell volume (% reduction)
1	No effect	No effect
2	No effect	No effect

Claims:

1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein R^o represents 2-benzoxazolyl or 2-pyridyl and R^1 represents CH_2OCH_3 or CF_3.

2. A compound according to claim 1, wherein R^o represents 2-benzoxazolyl.

3. A compound according to claim 1 or claim 2, wherein R^1 represents CF_3.

4. A compound according to claim 1 being:

(S)-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2-methoxy-ethoxy)propanoic acid;or

(S)-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-(2,2,2-trifluoroethoxy)propanoic acid; or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof.

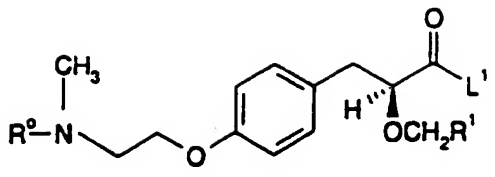
5. A compound according to any one of claims 1 to 4, when present in admixture with less than 50% w/w of its racemic isomer.

6. A compound according to any one of claims 1 to 5, when 90-100% optically pure.

7. A compound according to any one of claims 1 to 6, in optically pure form.

8. A process for the preparation of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable hydrate thereof, which process comprises:

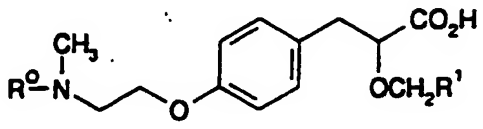
(a) hydrolysing a compound of formula (II):



(II)

wherein R^o and R^1 are as defined in relation to formula (I) and L^1 represents a hydrolysable group; or

(b) resolving a racemic compound of formula (VII):



(VII)

wherein R^o and R^1 are as defined in relation to formula (I); and thereafter, if required, preparing a pharmaceutically acceptable salt of the compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

9. A pharmaceutical composition comprising a compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier therefor.

10. A method for the treatment and/or prophylaxis of hyperglycaemia in a human or non-human mammal which comprises administering an effective, non-toxic, amount of a compound of the general formula (I), or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, to a hyperglycaemic human or non-human mammal in need thereof.

11. A method for the treatment of hyperlipidaemia, hypertension, cardiovascular disease, certain eating disorders, the treatment and/or prophylaxis of renal disease, the prevention, reversal, stabilisation or retardation of the progression of microalbuminuria to albuminuria in a human or non-human mammal, which comprises administering an effective, non-toxic, amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, to a human or non-human mammal in need thereof.

12. A compound of formula (I), or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use as an active therapeutic substance.

13. A compound of formula (I), or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment f and/or prophylaxis of hyperglycaemia, hyperlipidaemia, hypertension, cardiovascular disease, certain eating disorders, the treatment and/or prophylaxis of renal disease and/or the prevention, reversal, stabilisation or retardation of the progression of microalbuminuria to albuminuria.

14. The use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of hyperlipidaemia, hypertension, cardiovascular disease or certain eating disorders, the prophylaxis of renal disease and/or the prevention, reversal, stabilisation or retardation of the progression of microalbuminuria to albuminuria.

15. An intermediate compound of formula (II) or (III).

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/EP 95/03038

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D263/58 C07D213/74 A61K31/42 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,94 01420 (SANOFI) 20 January 1994 cited in the application see claims; examples 37,58	1-15
A	WO,A,91 19702 (PFIZER INC) 26 December 1991 see claims	1-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 October 1995	17. 10. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Henry, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 95/03038

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 10 and 11 are directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compounds.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/EP 95/03038

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